presented in Figure 4. When cancer death rates are examined by birth cohort (Figure 5), no decline with age can be demonstrated. The explanation for this seeming discordance in the data is the differences in pattern of cigarette smoking in different birth cohorts in the U.S. population (Figure 6) (US DHHS 1982). Those birth cohorts that currently represent the oldest age groups have lower smoking prevalences than the birth cohorts in the younger ages (those born between 1910 and 1930), and this decreased smoking prevalence resulted in a decreased lung cancer mortality. The risk ratios presented in Figure 3 are comparisons with the risk in the general population, and therefore represent the combined effect of the increased smoking prevalence among asbestos workers and the increased risk due to the asbestos exposure. To the extent that the age-related changes in smoking prevalence among older asbestos workers presented in Table 9 represent a return toward or below the smoking prevalence in the general population, a decline in the risk ratio among older asbestos workers would be expected. Regardless of the reason for the change in risk ratio among older workers (i.e., either differences in smoking behavior or decline in risk following cessation of asbestos exposure), the magnitude of the decline is modest, particularly when the rapidly increasing baseline risk of lung cancer in the general population with increasing age used to calculate these risk ratios is considered.

A somewhat different approach to this question was taken by Seidman and colleagues (1979), who examined the mortality experience of a group of workers exposed to asbestos over a very limited period of time during World War II and followed them for 35 years after the onset of this exposure. These workers had an extremely intense exposure to asbestos, but only very brief exposures with no subsequent asbestos work-exposure history. If the risk of lung cancer declines significantly following the cessation of exposure to asbestos, then these workers would be expected to have a declining risk of developing lung cancer with increasing duration from the onset of asbestos exposure. Figure 7 shows the ratio of observed to expected lung cancer deaths for the 10-year periods beginning 5, 15, and 25 years after the onset of exposure in workers who had worked less than 9 months and those who had worked more than 9 months in this plant. In both cases the risk is greater in workers for the 10-year period beginning 25 years after onset of exposure than for the period beginning 15 years after exposure. The small number of deaths recorded in the study limits its interpretation; however, the data are consistent with the conclusion that cessation of asbestos exposure may not be associated with a decline in the relative risk of developing lung cancer with increasing duration of time since last exposure.

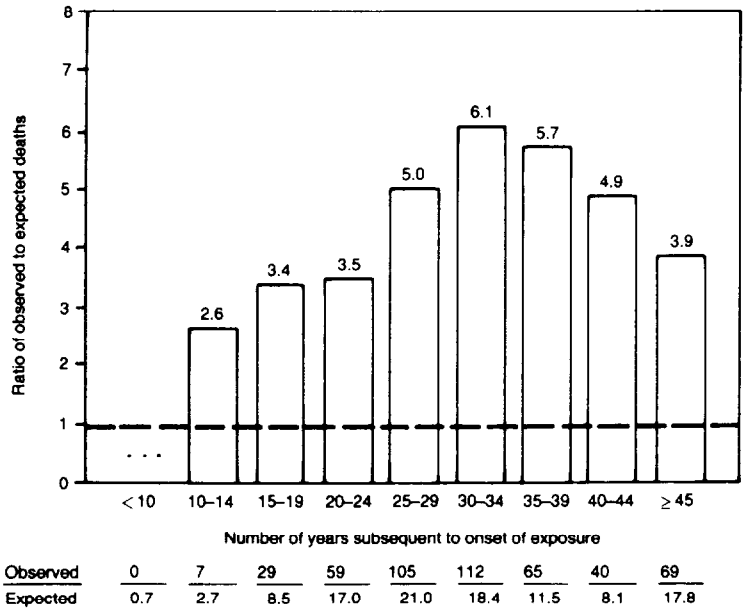

FIGURE 3.—Ratios of observed to expected deaths from lung cancer among 17,800 asbestos insulation workers observed prospectively, 1967 and 1976, in 5-year periods subsequent to beginning employment in this trade

NOTE: The decline in ratios after the 30- to 35-year period may be the result of a "survivor effect," because deaths associated with cigarette smoking (e.g., myocardial infarction, lung cancer) tend to selectively change the composition of the surviving cohort in relation to smoking status with time.

SOURCE: Selikoff, Hammond et al. (1980).

A similar result was reported by Blot and colleagues (1980) in a case–control study of male lung cancer patients. They found a small excess risk of developing lung cancer in workers who had been employed in shipyards for only a few years during World War II, and the relative risk in these workers was similar to that for workers who had worked regularly in the shipyards.

In summary, the data suggest that elimination of further asbestos exposure may prevent the further increase in relative risk that would accompany an increase in cumulative exposure. However, the relative risk of developing lung cancer persists even after prolonged avoidance of additional asbestos exposure. In contrast, the cessation of cigarette smoking appears to reduce the risk of developing lung cancer in asbestos insulation workers compared with those workers who continue to smoke, and the time course of this reduction in risk

TABLE 8.—Changes in the ratio of observed to expected deaths with time since first employment, four cohort studies

Years since initial exposure	North American insulators[1]		Quebec miners and millers[2]		Factory workers[3]		New York–New Jersey insulators[4]		Asbestos cement workers[5]	
≤ 10	2.55	(7)					0.00	(0)	0.77	(1)
11–15	3.40	(29)							1.25	(3)
16–20	3.48	(59)	0.00	(0)	2.38	(4)	8.67	(26)	1.54	(6)
21–25	5.00	(105)							2.33	(7)
26–30	6.08	(112)	1.94	(7)	3.73	(23)			3.33	(5)
31–35	5.68	(65)					6.63	(67)	3.08	(4)
36–40	4.93	(40)	4.19	(16)	1.37	(6)				
41–45	3.89	(69)								
46–≥ 50			1.67	(5)						
Total number of deaths		(486)		(28)		(33)		(93)		(26)

[1] Data from Selikoff, Hammond et al. (1980).
[2] Data from Nicholson et al. (1979).
[3] Data from Nicholson et al. (1979).
[4] Data from Selikoff et al. (1979).
[5] Data from Weill et al. (1979).
NOTE: Number of deaths given in parentheses.
SOURCE: Walker (1984).

is similar to that found among smokers in the general population who stop smoking.

Mechanisms of Carcinogenesis in Cigarette-Smoking Asbestos Workers

An increased risk of developing lung cancer has been observed with all commercially used types of asbestos. Most studies indicate that crocidolite exposure may produce a higher human lung cancer risk than chrysotile (Weill et al. 1979; Enterline and Henderson 1973), but some studies have shown the opposite (McDonald et al. 1983a, b; Dement et al. 1982). All of the four major histologic types of bronchogenic carcinoma develop in asbestos workers who smoke (Churg 1985; Auerbach et al. 1984; Whitwell et al. 1974). Although an increased risk of lung cancer with exposure to asbestos in nonsmokers has been demonstrated in a number of epidemiologic studies (Hammond et al. 1979; McDonald et al. 1980), it remains unclear whether the asbestos fiber by itself acts as a complete carcinogen for lung cancer in the respiratory tract of man. This is in contrast to the role of asbestos as a carcinogen in mesothelioma,

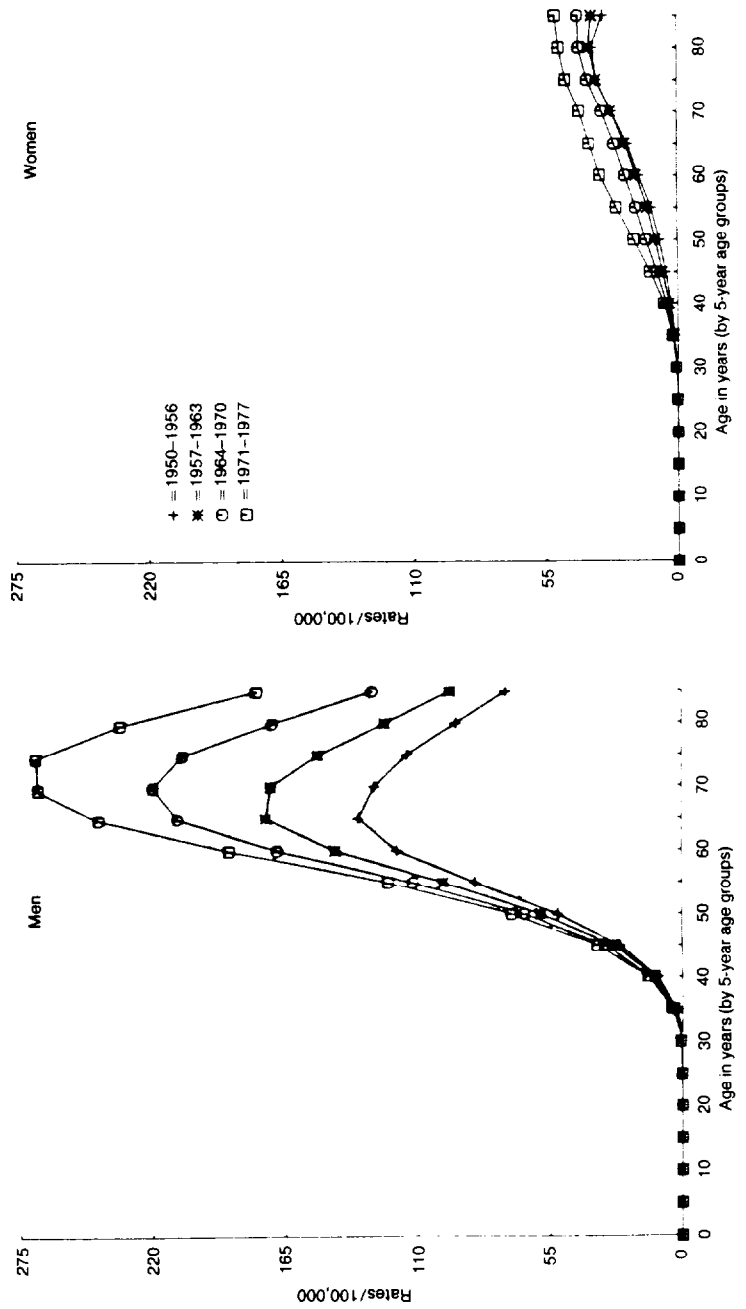

FIGURE 4.—Age-specific mortality rates for cancer of the bronchus, trachea, and lung, white men and women, United States

SOURCE: McKay et al. (1982).

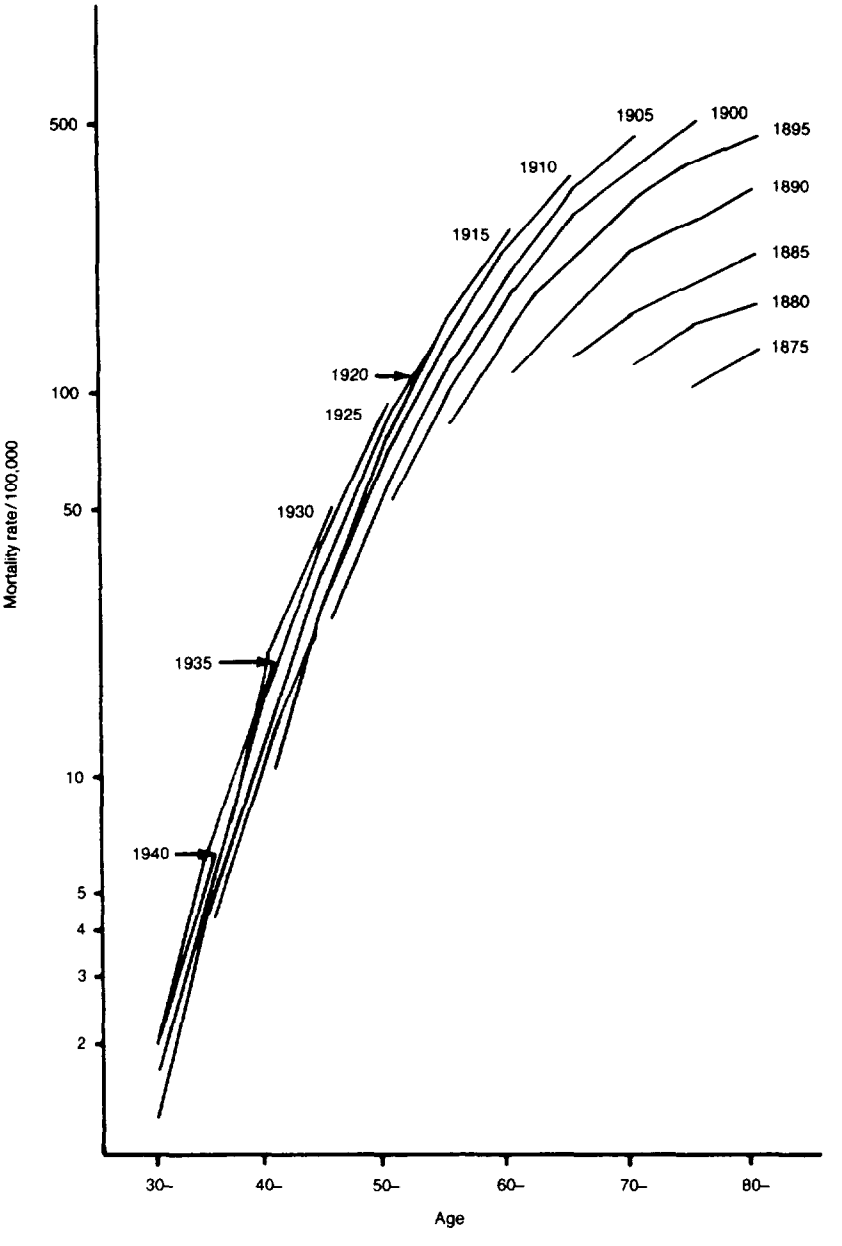

FIGURE 5.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death, men, United States, 1950–1975

SOURCE: Data derived from McKay et al. (1982).

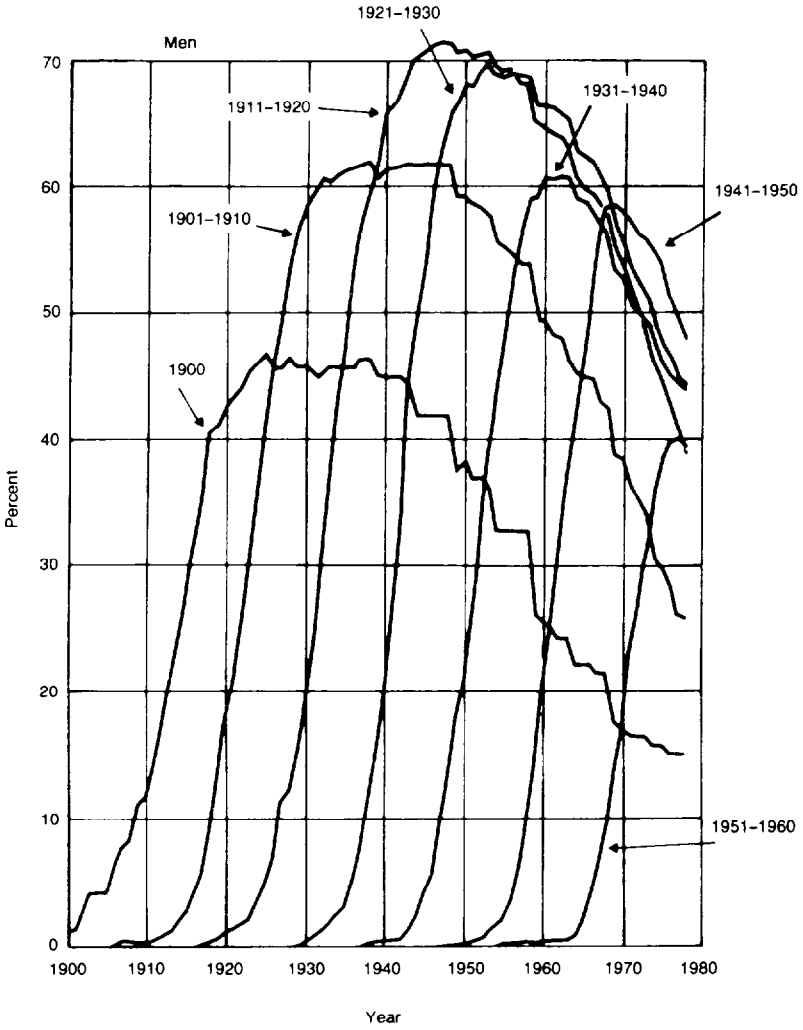

FIGURE 6.—Changes in the prevalence of cigarette smoking among successive birth cohorts of men, 1900–1978

NOTE: Calculated from the results of more than 13,000 interviews conducted during the last two quarters of 1978, provided by the National Center for Health Statistics, Division of Health Interview Statistics.
SOURCE: US DHHS (1982).

where asbestos exposure alone is clearly able to produce the tumor and where cigarette smoking does not alter the mesothelioma risk.

Laboratory investigations have been undertaken to evaluate the mechanisms through which asbestos interacts with the combustion products of cigarettes to induce neoplasms. In this regard, the carcinogenic properties of polycyclic aromatic hydrocarbons (PAH), documented chemical carcinogens in cigarette smoke, have been

TABLE 9.—Prevalence of smoking among asbestos insulation workers whose smoking history was known

Age	Current smokers	Former smokers	Never smoked regularly	Pipe and cigar
25–29	64.8	19.3	13.0	2.9
30–34	61.0	19.3	13.5	6.[illegible]
35–39	60.9	22.2	11.6	4.9
40–44	61.3	25.0	9.2	4.5
45–49	55.8	28.8	9.8	5.6
50–54	53.7	32.2	9.1	5.0
55–59	50.1	34.1	9.8	6.0
60–64	45.4	35.1	10.4	9.1
65–69	42.3	33.7	12.4	11.6
70–74	30.7	34.3	17.5	17.5
75–79	51.5	34.3	7.1	7.1
80–84	37.1	33.3	11.1	18.5
≥85	30.0	35.0	25	10.0

Source: Hammond et al. (1979).

evaluated in combination with asbestos both in tissue cultures and in grafts of respiratory tract epithelium (reviewed in Craighead and Mossman 1982; Mossman, Light et al. 1983). This section summarizes the results of these experimental studies.

Animal Studies of the Carcinogenic Interactions Between Cigarette Smoke and Asbestos

When animals are administered asbestos in inhalation chambers or by intratracheal instillation, differences among species and strains appear to influence the occurrence of lesions. For example, only benign lesions (papillomas and adenomas) are found in hamsters, guinea pigs, and rabbits after prolonged inhalation of asbestos (Botham and Holt 1972a, b; Gardner 1942; Reeves et al. 1974), whereas cats (Vorwald et al. 1951) and nonhuman primates (Wagner 1963; Webster 1970) develop fibrosis of the lung but not tumors. Small numbers of neoplasms (squamous cell carcinoma, adenocarcinoma, small and large cell carcinoma) have been reported in rats (Davis et al. 1978; Reeves 1976; Reeves et al. 1974; Wagner et al. 1974), but benign neoplasms and fibrosarcomas (tumors rare in the human lung) predominate. Mice also appear to develop both benign and malignant tumors after inhalation of asbestos (Bozelka et al. 1983; Gardner 1942). Bozelka and colleagues (1983) found a large

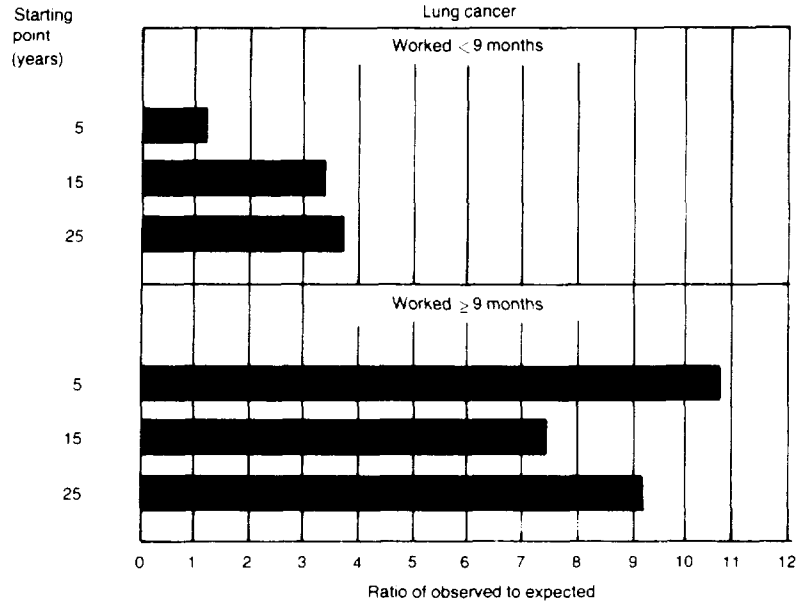

FIGURE 7.—Observed compared with expected weighted average probabilities of lung cancer death in 10-year periods, starting at 5-, 15-, and 25-year points after beginning of work in an amosite asbestos factory, 1941–1945, for men who worked less than or more than 9 months

NOTE: Computed by assigning weights of 55 and 45 percent to the probabilities given in Seidman and colleagues (1979) for men aged 40 to 49 and 50 to 59, respectively, at the start of the 10-year periods.
SOURCE: Seidman et al. (1979).

number of lesions of questionable malignancy in the lungs of Balb/c mice 12 to 18 months after a 75-day exposure to chrysotile asbestos.

Unfortunately, it is difficult to evaluate many of these animal studies critically because satisfactory controls were not employed and data on exposure regimens and concentrations of asbestos are often not available. In addition, adequate pathologic documentation of the lesions is often lacking. Benign adenomas could occur spontaneously in many lesser species (Mitruka et al. 1976), and luxuriant squamous metaplasia and bronchiolization of the respiratory mucosa may be misinterpreted as malignant lesions. These last epithelial changes may occur as a response to injury induced by asbestos (Davis et al. 1978; Mossman et al. 1980; Reeves et al. 1974; Wagner 1963; Woodworth et al. 1983a, b).

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Several investigators have administered chrysotile to rats and hamsters in combination with either cigarette smoke or benzo[a]pyrene (BaP), a major polycyclic aromatic hydrocarbon (PAH) in cigarette smoke (Table 10) (Miller et al. 1965; Pylev and Shabad 1973; Shabad et al. 1974; Smith et al. 1968; Wehner et al. 1975). A striking increase in neoplasms (both benign and malignant) of the respiratory tract was observed. In contrast, a synergistic effect on tumor development was not apparent in rats exposed to asbestos and cigarette smoke by inhalation (Shabad et al. 1974; Wehner et al. 1975); however, the majority of the animals in these studies died prematurely of pulmonary fibrosis.

The effects of asbestos on the carcinogenicity of PAH in the respiratory tract have been evaluated using grafts of tracheal tissue implanted into syngeneic animals. Two model systems have been developed. In the first, the tracheas of rats are excised and formed into tubular sacs by ligatures at the ends and then transplanted subcutaneously (Topping and Nettesheim 1980; Topping et al. 1980). When relatively large amounts of chrysotile are introduced into the lumina of these grafts, inflammatory changes appear and fibrosarcomas develop in a substantial proportion of animals (Topping et al. 1980). On the other hand, epithelial tumors (carcinomas) appear when low concentrations of the PAH dimethylbenz[a]anthracene are introduced into the tracheal grafts before chrysotile (Topping and Nettesheim 1980). The amounts of PAH used in these experiments were insufficient to cause tumors; therefore, the asbestos acted as a promoting agent.

In the second model system, organ cultures of hamster trachea are exposed to crocidolite asbestos and implanted into syngeneic recipients after various periods of incubation in vitro (Craighead and Mossman 1979; Mossman and Craighead 1979, 1981, 1982). Neoplasms failed to develop in these experiments. However, tumors, the majority of which were carcinomas, were found when the PAH 3-methylcholanthrene (3MC) was coated on the surface of the crocidolite fibers and precipitated onto the epithelial surfaces of the tracheal organ cultures prior to transplantation. This tissue served as the nidus for the development of squamous cell carcinomas in the hamsters implanted with the cultures. In these experiments, asbestos appeared to be a carrier of PAH, because 3MC also produced tumors when absorbed to nonfibrous particulates such as kaolin, hematite, and carbon (Mossman and Craighead 1979, 1982).

Concepts of Carcinogenesis

The concepts of initiation and promotion were developed to explain the complex, multistep process of chemical carcinogenesis. "Initiation" is defined as the irreversible DNA damage of a cell induced by a carcinogenic agent. In contrast, tumor "promotion" is a

TABLE 10.—Tumors occurring in rodents after exposure to asbestos in combination with components of cigarette smoke

Number of tumors/Number of animals					
Chrysotile	Agent alone	Combination	Tumor types	Animal	Reference
Inhalation					
5/51	12/51 (smoke)	9/51 (+smoke)	Adenoma, papilloma, carcinoma	Rat	Wehner et al. (1975)
0/46	ND[1]	0/16 (+smoke) 0/21 (+BaP[2])	ND	Rat	Shabad et al. (1974)
Intratracheal instillation					
ND	8/37 (BaP)	18/35 (+BaP)	Adenoma, papilloma, carcinoma	Hamster	Smith et al. (1968)
0/17	10/34 (BaP)	24/31 (+BaP)	Adenoma, papilloma, carcinoma	Hamster	Smith et al. (1968)
0/49	0/19 (BaP)	6/11 (+BaP mixed) 6/21 (+BaP adsorbed)	Adenoma, carcinoma, reticulosarcoma, mesothelioma	Rat	Pylev and Shabad (1973)
0/10	4/10 (BaP)	15/10[3] (+BaP)	Papilloma, carcinoma	Hamster	Miller et al. (1965)

[1] ND = no details provided.

[2] BaP = benzo[a]pyrene.

[3] Animals developed multiple tumors.

sequential process whereby a second, but unrelated, generally noncarcinogenic substance acts to enhance the effect of an initiator. Initiated cells undergo proliferative changes and differentiation that ultimately result in transformation to a malignant lesion. Much of the information that has accumulated on classical tumor promoters and their mechanisms of action was derived from studies with mice in which the animal's skin was painted with PAH, followed by repeated applications of phorbol esters (or related compounds) (reviewed in Slaga et al. 1982). Nonetheless, the concepts of initiation and promotion appear broadly relevant to carcinogenesis in the mammary gland, liver, colon, urinary bladder, brain, and lung (Marx 1978). In this regard, a wide variety of chemical, physical, and infectious agents interact with tissues to induce a constellation of inflammatory and proliferative changes ultimately resulting in malignancy.

It is doubtful that the action of asbestos in increasing lung cancer risk is as a tumor initiator (reviewed in Craighead and Mossman 1982; Mossman and Craighead 1981). Few epithelial tumors develop in experimental animals when PAH are not used in conjunction with asbestos. Moreover, chrysotile and crocidolite do not seem to damage the DNA of hamster or human tracheobronchial epithelial cells (Fornace 1982; Mossman, Eastman et al. 1983). In most (but not all) studies using cell culture systems, asbestos is neither mutagenic nor carcinogenic (Chamberlain and Tarmy 1977; Daniel 1983; Kaplan et al. 1980; Reiss et al. 1982), but the malignant transformation of hamster embryo fibroblastic cells by asbestos, glass fibers, and silica particles has been reported recently (Hesterberg and Barrett 1984; Oshimura et al. 1984). Under these circumstances, asbestos may not act like a classical mutagen, but appears to cause alterations in chromosomal structure (Barrett et al. 1983), perhaps consequent to its cytotoxic effects.

In contrast, asbestos exhibits many of the properties of classical tumor promoters when introduced into grafts of tracheal tissue (Topping and Nettesheim 1980) and monolayer cultures of hamster and human tracheobronchial tissues (reviewed in Craighead and Mossman 1982; Mossman and Craighead 1981; Mossman, Light et al. 1983). Like the phorbol esters, asbestos appears to induce perturbations of the plasma membranes of cells, such as the stimulation of membrane-associated enzymes (Mossman et al. 1979) and the generation of oxygen free radicals (Mossman and Landesman 1983). In addition, both asbestos and fibrous glass induce the biosynthesis of polyamines, important biochemical markers of cell division and proliferative changes in the tracheobronchial mucociliary epithelium (Landesman and Mossman 1982; Marsh and Mossman 1984). This is accompanied by the development of squamous metaplasia, a putative premalignant change. These alterations in cell function and

structure are not observed in tissues exposed to nonfibrous mineral analogs of asbestos and glass, an observation indicating that the fibrous geometry of the material is important (Woodworth et al. 1983b).

Cigarette smoke contains ciliostatic and toxic chemicals that impair mucociliary transport and the function of phagocytic cells (Warr and Martin 1978). Thus, intrapulmonary deposition and clearance of asbestos might be affected, resulting in increased retention of asbestos in the lungs. In addition, the development of squamous metaplasia consequent to exposure to both PAH and asbestos (Mossman et al. 1984) might contribute to the retention in the respiratory tract of asbestos and the constituents of cigarette smoke.

Studies using artificial membranes and cells in culture suggest other possible mechanisms of synergism between PAH and asbestos. PAH are not carcinogenic in their natural state and must be metabolized by a mixed-function, microsomal enzyme system (aryl hydrocarbon hydroxylase, AHH) to degradative products and electrophilic forms interacting with DNA (Freudenthal and Jones 1976). In this regard, the association (adduct formation) of modified metabolites of PAH with the DNA of "target" cells is thought to be a critical event in initiation of those cells. A number of studies suggest that the addition of asbestos and PAH to tracheobronchial epithelial cells (Mossman and Craighead 1982), microsomal preparations from lungs (Kandaswami and O'Brien 1981), and phagocytes (McLemore et al. 1979) affects the normal metabolism of PAH as measured by an increase (or decrease) in activity of AHH enzymes. Unfortunately, these results are inconsistent, possibly a reflection of the different experimental systems evaluated. Accordingly, this important area of carcinogenesis needs further exploration.

PAH are ubiquitous in the environment and are associated with airborne particulates (Natusch et al. 1974). Thus, the ability of asbestos and other particles to act as "condensation nuclei" for chemical carcinogens has been explored using tracheobronchial epithelial cells (Mossman, Eastman et al. 1983; Eastman et al. 1983) and artificial or isolated cell membranes (Lakowicz and Bevan 1979; Lakowicz et al. 1978). Transfer of PAH to cell membranes by asbestos appears to occur more rapidly than with use of nonfibrous particulates (Lakowicz and Bevan 1979; Lakowicz et al. 1978). Moreover, the normal uptake of BaP and the formation of BaP-DNA adducts by tracheal epithelial cells are increased when BaP is adsorbed to chrysotile and crocidolite asbestos (Mossman, Eastman et al. 1983; Eastman et al. 1983).

The pulmonary alveolar macrophage (PAM) is a key cell in the response of the host to asbestos. PAMs accumulate at sites of deposition of asbestos in the tracheobronchial tree (Brody et al.

1981), a process associated with activation and release of lysosomal enzymes (Davies et al. 1974) and the generation of oxygen free radicals (McCord and Wong 1979). In addition, these cells possess the enzymatic capability to convert PAH to active metabolites (Autrup et al. 1978) and may facilitate the transfer of hydrocarbons to tracheobronchial epithelial cells and other cell types (Shatos and Mossman 1983). Thus, either damage to or activation of macrophages by asbestos and the components of cigarette smoke could influence the process of carcinogenesis.

Conclusions

Several mechanisms by which cigarette smoke and asbestos may interact to increase carcinogenic risk are possible, but they remain unproved in man. First, asbestos fibers could serve as carriers of the carcinogens of cigarette smoke into the cell. Physical transport of this type has been demonstrated experimentally, and there is evidence to suggest that asbestos transfers PAH to cell membranes with unusual efficiency in comparison with other particulates. While this mechanism is an intriguing possibility, it presupposes the interaction of smoke constituents with aerosols of asbestos fibers in the atmosphere. Events of this nature remain hypothetical and unproved. A second mechanism is based on experimental evidence accumulated in both animals and cell culture systems. In this schema, asbestos serves as a promoter in the respiratory epithelium to alter the properties of the epithelial cells and to enhance neoplastic transformation in cells initiated by the combustion products of cigarettes. Biological evidence supporting this mechanism of carcinogenesis is compelling in experimental models of carcinogenesis, but not easily tested in man.

The possible role of macrophages in the metabolism of PAH adsorbed to asbestos is an intriguing consideration. These cells are biologically activated in the smoker and in the lungs of those exposed to asbestos. They frequently accumulate in large numbers in the airspaces of individuals exposed to these and other pollutants. One can only speculate on whether or not the alveolar macrophage contributes to the metabolism of chemical carcinogens under these circumstances.

Although obvious information gaps exist, consideration of the experimental results described here and the contemporary concepts of neoplastic transformation suggest several mechanisms of interaction between components of cigarette smoke and asbestos. On the one hand, asbestos appears to resemble a classical tumor promoter after initiation of tracheobronchial epithelial cells by the carcinogenic chemicals found in cigarette smoke. Alternatively, asbestos appears to act as a vehicle for the transfer of PAH across cell membranes and affects the metabolism of these carcinogens, factors

favoring the process of initiation. Finally, asbestos and the toxic constituents of cigarette smoke injure cells, a situation potentially encouraging the retention of these inhalants in the respiratory tract.

Chronic Lung Disease

Cigarette smoke (US DHHS 1984) and asbestos exposure (Selikoff and Lee 1978) are well-established causes of chronic lung injury. As in the preceding discussion of lung cancer, the enormous body of literature that established the pathogenicity of each of these agents is not presented; rather, this section focuses on the effects of combined exposure. In contrast to their effect on the risk of developing lung cancer, asbestos and cigarette smoke produce different patterns of injury in the lung. The pattern of lung injury associated with cigarette smoking is characterized by inflammation, excess mucus production, narrowing of the airway lumen, and emphysema (US DHHS 1984). The result is a reduction in maximal expiratory flow rates and increased static lung volumes. The pattern of lung injury associated with asbestos is fibrosis of the small airways extending into the alveolar structures with obliteration of alveoli, leading to a reticular nodular pattern of interstitial fibrosis on chest roentgenogram and decreased lung volumes, with relative preservation of the forced expiratory volume in 1 second (FEV_1) as a percent of the forced vital capacity (FVC) (Selikoff and Lee 1978).

In spite of these relatively distinct patterns of lung injury, interpretation of the pattern of injury in combined exposure is difficult. Both agents may act separately, but simultaneously, to injure the lung. The injury in an individual worker is the combination of the injuries due to cigarette smoke, asbestos and other environmental agents, and all other injurious processes that have occurred during that individual's lifetime. The presence of a lung injury secondary to one agent or process does not prevent the lung from being injured by a second agent. In evaluating impairment in an asbestos-exposed smoker, it may be difficult to apportion the impairment between the two agents because both cigarette smoking and asbestos exposure may alter a given lung function test in the same direction (e.g., both of them reduce the diffusing capacity (DLCO)), or they may change a test in opposite directions (e.g., an increase in total lung capacity (TLC) due to smoking may mask a decline in TLC due to asbestos). When a given physiologic test is influenced in opposite directions by cigarette smoking and asbestos, the degree of injury to the lung may be underestimated by the change in that test. For example, the relative preservation of TLC in cigarette-smoking asbestos workers does not represent a relative protection of the lung in combined exposure, but rather reflects the emphysematous destruction of alveolar walls secondary to cigarette

smoking (which increases TLC) being combined with the asbestos-related fibrosis and obliteration of other alveolar units (which reduces TLC).

Interstitial fibrosis of the lung is a well-described and well-established sequel of heavy asbestos exposure. In an individual, the fibrosis is attributed to asbestos when a pattern of lung injury on chest roentgenograph or lung biopsy consistent with that found in asbestos-exposed populations is found in conjunction with a history of significant asbestos exposure or with levels of asbestos in lung tissue consistent with significant asbestos exposure. Fibrosis due to other causes such as exposure to coal dust, silica, or infection needs to be considered in evaluating individual patients, and both diagnosis and attribution to a specific etiologic agent may be difficult in the very early stages of the fibrotic process. However, by the time the process has progressed to the degree that it causes significant disability or death, the diagnosis is usually readily evident and the substantial asbestos exposure generally necessary to cause this degree of fibrosis is also easily identifiable.

Chronic Lung Disease Death Rates

Cigarette-induced chronic lung injury does not produce the extensive fibrosis commonly found in individuals dying of asbestos-induced interstitial fibrosis, and therefore does not interfere in the diagnosis, or attribution to asbestos, of the severe fibrotic lung disease in these individuals. However, cigarette smoking can cause significant lung destruction and disability, and therefore it may contribute to the mortality and degree of disability in individuals with asbestos-induced interstitial fibrosis, independent of any effect of cigarette smoking on the degree or extent of fibrosis. In addition, because death and disability occur only after extensive lung injury, the independent (i.e., additive) lung injuries due to smoking and asbestos might sum to produce a level of disability that could exert a synergistic effect on death rates.

Frank (1979) presented data on the death rates in smoking and nonsmoking asbestos insulation workers (Table 11). The population was drawn from the 17,800 asbestos insulation workers studied by Hammond and colleagues (1979) and included those workers with more than 20 years of exposure whose smoking habits were known. The age-standardized death rates from chronic lung disease (including asbestosis) were increased by either cigarette smoking or asbestos exposure, and the rate in cigarette-smoking asbestos workers was well above the sum of the rates for non-asbestos-exposed smokers and nonsmoking asbestos workers. This "synergism" was also present when only asbestosis deaths were considered, with the death rate almost three times higher in cigarette-smoking asbestos workers than in nonsmoking asbestos workers. This study revealed a

greater than additive effect for cigarette smoking and asbestos exposure on death rates from chronic lung disease and asbestosis. This may reflect a "synergistic" effect on death rates of the "addition" of the two separate injuries, rather than an effect of cigarette smoking on the degree of fibrosis produced by a given dose of asbestos. In addition, these data reflect the fact that a death certification of asbestosis does not rule out the possibility of a second disease process existing in the lungs of that individual.

Pulmonary Function Testing

The most frequently used measures of lung function are lung volumes and measures of maximal expiratory airflow, either as the volume expired during a given time (e.g., forced expiratory volume in 1 second, FEV_1) or as the rate of expiratory airflow at a given lung volume or between two lung volumes (e.g., forced expiratory flow from 25 to 75 percent of the forced vital capacity, $FEF_{25-75\%}$). Classically, diseases are divided by their pattern of abnormality on lung function testing into obstructive (processes that predominately limit expiratory airflow) and restrictive (processes that predominately decrease lung volumes and specifically decrease the total lung capacity). Both of these processes may occur in a single individual, resulting in a mixed pattern (both reduced lung volumes and reduction in volume-adjusted expiratory flow rates).

Obstructive lung disease is marked by reductions in the rate of expiratory airflow; normal or, more typically, increased TLC; and substantial increases in residual volume (RV) and functional residual capacity (FRC) (Figure 8). Restrictive diseases are marked by a reduction in TLC. The flow rates in restrictive disease are usually normal or even increased once an adjustment for the decreased lung volume has been made. FEV_1 is obviously limited by the total volume that can be expired, as well as by the amount of obstruction to expiratory airflow. For this reason, FEV_1 is commonly divided by the forced vital capacity (FVC), and expressed as the percentage of the FVC that can be expired in 1 second ($FEV_1/FVC\%$). This adjustment of FEV_1 for reductions in FVC aids in separating the decline in FEV_1 that is due to a restrictive process (i.e., reduced TLC) from that which represents increased resistance to, and decreased driving pressure for, expiratory airflow.

The pattern of lung function change in cigarette smokers has been well described (US DHHS 1984), and consists of a reduced FEV_1 and $FEV_1/FVC\%$, an increased RV and FRC, and an increased TLC (particularly in those individuals with emphysema). In addition, $FEF_{25-75\%}$, DLCO, and flows at specific lung volumes are also usually reduced.

The pattern of change with the development of interstitial fibrosis due to asbestos is also clear. Figure 9 shows the changes in lung

TABLE 11.—Age-standardized death rates for combinations of cigarette smoking, no smoking, asbestos exposure, and no asbestos exposure; selected causes of death

Group	All causes	All cancer	Noninfectious pulmonary diseases (total includes asbestosis)	Asbestosis	All other causes
Death rates per 100,000 man-years					
I. No asbestos work and no smoking	980.9	208.2	28.8	—[1]	743.9
II. No asbestos work, but smoking	1580.7	353.1	103.8	—[1]	1123.8
III. Asbestos work and no smoking	1430.9	563.9	77.1	77.1	789.9
IV. Asbestos work and smoking	2659.0	1317.0	286.5	225.5	1005.5
Mortality ratios					
No asbestos work and no smoking (I ÷ I)	1.00	1.00	1.00		1.00
No asbestos work, but smoking (II ÷ I)	1.61	1.70	3.60		1.51
Asbestos work and no smoking (III ÷ I)	1.46	2.71	2.68		1.06
Asbestos work and smoking (IV ÷ I)	2.71	6.33	9.95		1.42
Excess in death rates					
V. Smoking only (II–I)	599.8	144.9	75.0	—[1]	379.9
VI. Asbestos work only (III–I)	450.0	355.7	48.3	77.1	46.0
VII. Synergism (IV–I–V–VI)	628.3	608.2	134.4	148.4	-114.3
Percent excess in death rates					
Smoking only (100V ÷ I)	61	70	260		51
Asbestos work only (100VI ÷ I)	46	171	168		6
Synergism (100VII ÷ I)	64	292	467		-15

NOTE: Rate per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos insulation workers ≥ 20 years after onset of asbestos work. Rates for the asbestos work-exposure groups are based on cause of death coded according to the best available evidence.

[1] Death rates not available for the no asbestos work-exposure groups.

SOURCE: Frank (1979).

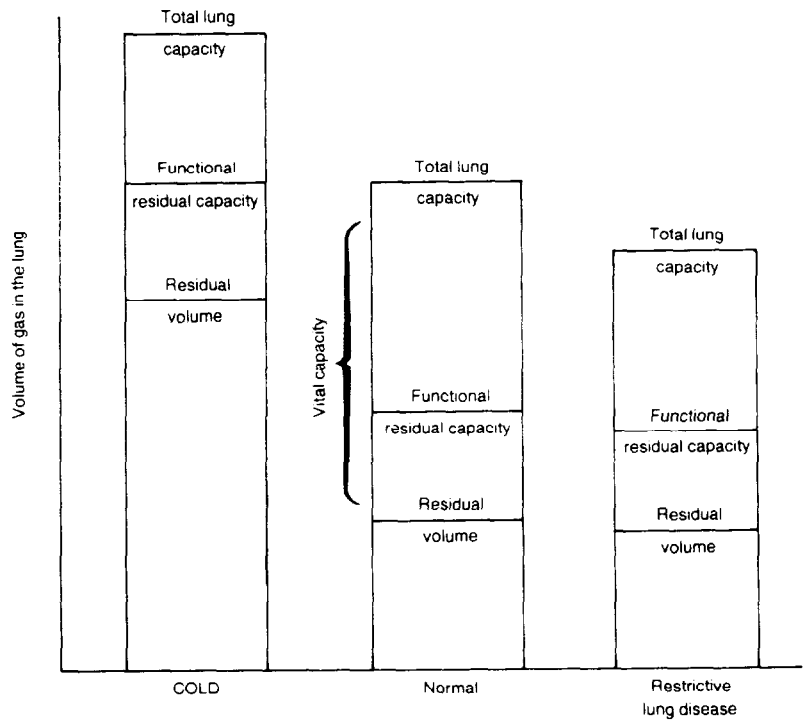

FIGURE 8.—Lung volumes in normal individuals and in patients with chronic obstructive lung disease and restrictive lung disease

volumes and Figure 10 shows the changes in the forced expiratory flow rates for the Quebec asbestos workers at several levels of increasing cumulative exposure to asbestos dust (Becklake et al. 1972). The lung function tests were performed on 1,027 men aged 21 to 65 who represented an age-stratified random sample of the 6,180 men employed in the Quebec asbestos mines and mills on October 31, 1966. An additional 184 men between the ages of 61 and 65 were also studied to increase the number of workers in the highest exposure categories. The data in the figures represent the averages of the test values for smokers and nonsmokers after they had been standardized for age, height, and weight. Smokers were defined as those who had ever smoked at least one cigarette per day for 1 year; therefore, this category includes former smokers.

The pattern in nonsmoking asbestos workers is that of restriction; there is a steadily declining TLC with increasing dust exposure.

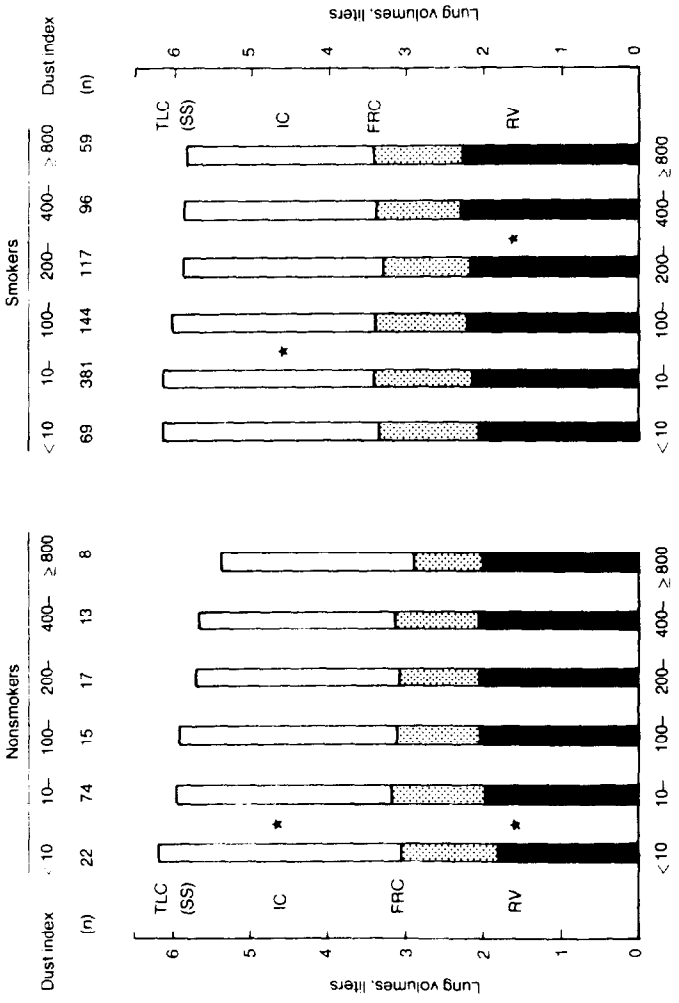

FIGURE 9.—Standardized mean values for subdivisions of lung volume (TLC[SS], IC, FRC, and RV) in nonsmokers and smokers, divided by dust index

NOTE: (n) = number of individuals in each subgroup.
SOURCE: Becklake et al. (1972).

FEV_1 also declines with increasing exposure, but this decline can be accounted for by the decline in FVC, as $FEV_1/FVC\%$ does not decline with increasing exposure in nonsmokers and is above 80 percent in all but the lowest exposure category. $FEF_{25-75\%}$ is also preserved in all but the two highest exposure categories. The FEF_{25-}

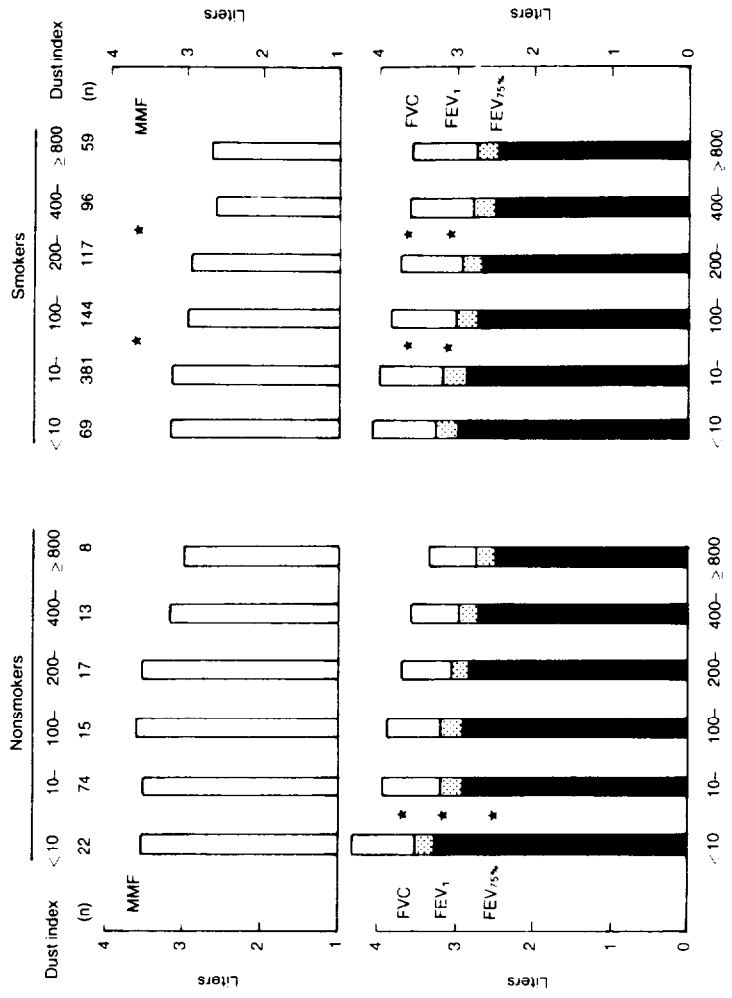

FIGURE 10.—Standardized mean values for flow rates (MMF, $FEV_{75\%}$, FEV_1, and FVC) in nonsmokers and smokers, divided by dust index

NOTE: (n) = number of individuals in each subgroup.
SOURCE: Becklake et al. (1972).

75% measurement would also be expected to decline with a fall in FVC, independent of any change in the degree of obstruction to airflow. Thus, in this group of nonsmoking asbestos workers, the pattern of asbestos-induced lung disease is a reduction in lung volumes with preservation of $FEV_1/FVC\%$.

The changes in lung function in the smoking asbestos workers in this study can be contrasted with those of nonsmoking asbestos workers with comparable cumulative exposure histories (Figures 9 and 10). The static lung volumes (Figure 9) are larger for smokers than nonsmokers at each level of cumulative asbestos exposure. $FEF_{25-75\%}$ and FEV_1 are lower, as is $FEV_1/FEV\%$. There is a progressive decline in $FEV_1/FVC\%$ with increasing cumulative asbestos exposure in the smokers but not in the nonsmokers. This decline is probably attributable to the increase in cumulative cigarette smoking exposure (and related injury) that occurs with increasing cumulative asbestos exposure (Rossiter and Weill 1974), because of the correlation between these cumulative measures. The picture that evolves from this study of the effect of combined cigarette smoke and asbestos exposure is one of an obstructive process superimposed upon a restrictive process. In addition, in the population of workers with relatively heavy asbestos exposure, TLC is reduced in both smokers and nonsmokers, suggesting that the restrictive pulmonary process exerts a greater effect than those changes that tend to increase TLC (e.g., emphysema). The relative preservation of TLC that occurs in cigarette-smoking asbestos workers in comparison with nonsmoking workers should not be interpreted as a protective effect of smoking, because it almost certainly represents more extensive lung damage (i.e., the combination of emphysematous and fibrotic processes) in the lungs of the cigarette smokers. It is also important to note that the data from this study show a relatively clear dose–response relationship between cumulative asbestos exposure and degree of restrictive impairment.

The pattern of lung function response in smoking and nonsmoking workers found in this study is consistent with the premise that asbestos exposure causes a relatively pure restrictive lung disease and cigarette smoking causes a relatively pure obstructive process. In combined exposure, the lung functional changes represent the combination of the effects of these two independent processes. A number of other studies have examined the lung function in smoking and nonsmoking asbestos workers, and the data from these studies can be used to explore this relationship further.

A general morbidity study was conducted of civilian naval dockyard workers in Great Britain, and lung function tests were performed on 612 male registered asbestos workers (Harries and Lumley 1977). The measurements were standardized to a height of 1.7 meters and to a constant age within each of five age ranges. Smoking habits were classified as smoker, nonsmoker, or ex-smoker. TLC showed no relationship to age, smoking status, or duration of asbestos exposure. There was a tendency for smokers to have a lower FEV_1 than nonsmokers, and the difference increased with age. FEV_1 and duration of asbestos exposure were related only for those aged

50 to 59. The differences in FVC between smokers and nonsmokers were less than the differences in FEV_1, demonstrating a relative preservation of FEV_1/FVC in nonsmokers, and a relationship between duration of exposure and FVC was again present only in the 50- to 59-year-old age group. The absence of a relationship between TLC and duration of exposure may be due to the somewhat lower intensity of asbestos exposure in this population in comparison with the Quebec miners.

In a companion study of the same naval dockyards, Rossiter and Harries (1979) examined the lung function in 1,200 men aged 50 to 59. The sample included all men in the register of asbestos workers, 1 in 3 of those currently in occupations where intermittent exposure to asbestos might occur, and 1 in 30 of the remainder. Lung function measurements were standardized to age 55 and a height of 1.7 meters. Smoking was characterized as nonsmoker, ex-smoker, or current smoker, and lung function was analyzed by duration of exposure to asbestos. FEV_1 was lower in the smokers than in the nonsmokers, and the workers in the registered asbestos-exposure group had lower values than workers in other occupational groups. This was particularly true of the group of asbestos laggers who had been employed prior to 1957. The differences in FVC among the different smoking habits were less than the differences for FEV_1. The FEV_1/FVC ratio was markedly influenced by smoking. Even among those workers employed before 1957, the FEV_1/FVC ratio was preserved in nonsmokers but declined among cigarette smokers.

Weill and colleagues (1975) adopted a somewhat different approach by developing predictive equations specific for the smoking status of the worker, as well as age and height, for the individual function tests. $FEF_{25-75\%}$ was lower and declined more rapidly in smokers than in nonsmokers (Figure 11) in the population used to develop the predictive equations. The researchers applied these smoking-specific regression equations to 859 workers who were employed in two asbestos manufacturing plants in New Orleans on November 3, 1969. Dust exposure measurements were derived from midget impinger samples taken between 1952 and 1969 and from estimates of exposures derived from interviews with employees who had worked prior to this time period. Figures 12 and 13 reveal a decline in TLC with increasing cumulative asbestos exposure; as would be expected, this decline is accompanied by declines in the vital capacity, FEV_1, and $FEF_{25-75\%}$. However, there is no decline in FEV_1/FVC with increasing duration of exposure. The decline in TLC and vital capacity at the lower exposure levels occurred entirely in the group with x-ray changes, but for the two highest exposure categories, the decline in TLC and vital capacity occurred even in the group with no roentgenographic changes. Again, this study suggests that the effect of asbestos dust exposure in a manufacturing plant is

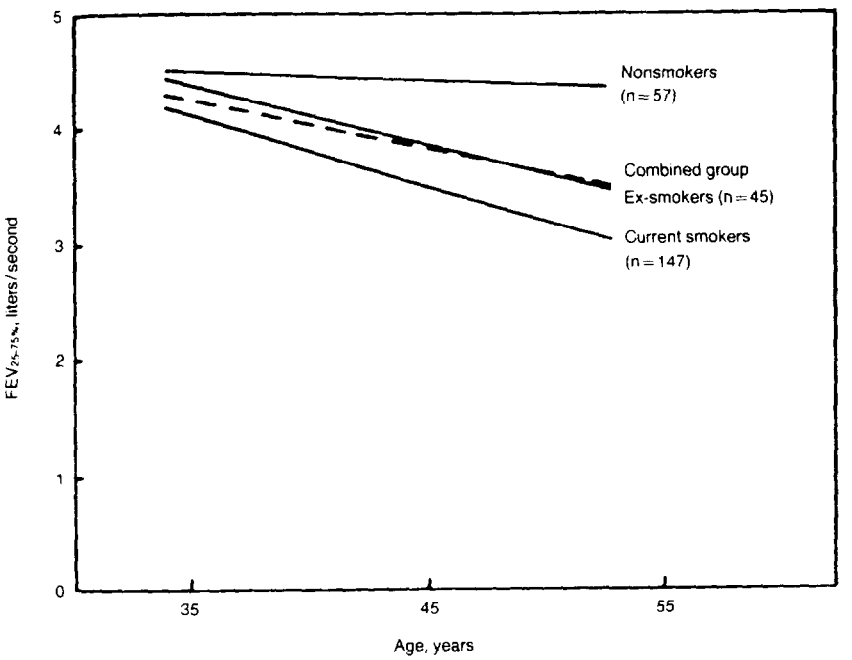

FIGURE 11.—Relationship between $FEV_{25-75\%}$ and age for the smokers, ex-smokers, and nonsmokers in the standard group (height taken as 175 cm [5 feet 9 inches])

SOURCE: Weill et al. (1975).

largely that of a restrictive process producing a decline in TLC, with the decline in FEV_1 and maximal midexpiratory flow between 25 and 75 percent of FVC ($MMF_{25-75\%}$) being a reflection of the decline in lung volumes rather than an indication of the presence of airflow obstruction.

Several analyses have focused on the pattern of pulmonary function response rather than on isolated test values (Fornier-Massey and Becklake 1975, Becklake et al. 1976; Muldoon and Turner-Warwick 1972; Murphy et al. 1972, 1978). These authors were attempting to determine whether asbestos exposure results in chronic obstructive lung disease, either in the absence of cigarette smoking or in excess of the level to be expected solely from smoking. The stratified sample of 1,027 Quebec asbestos miners and millers described earlier in this section was also analyzed by the pattern of pulmonary function response (Fornier-Massey and Becklake 1975;

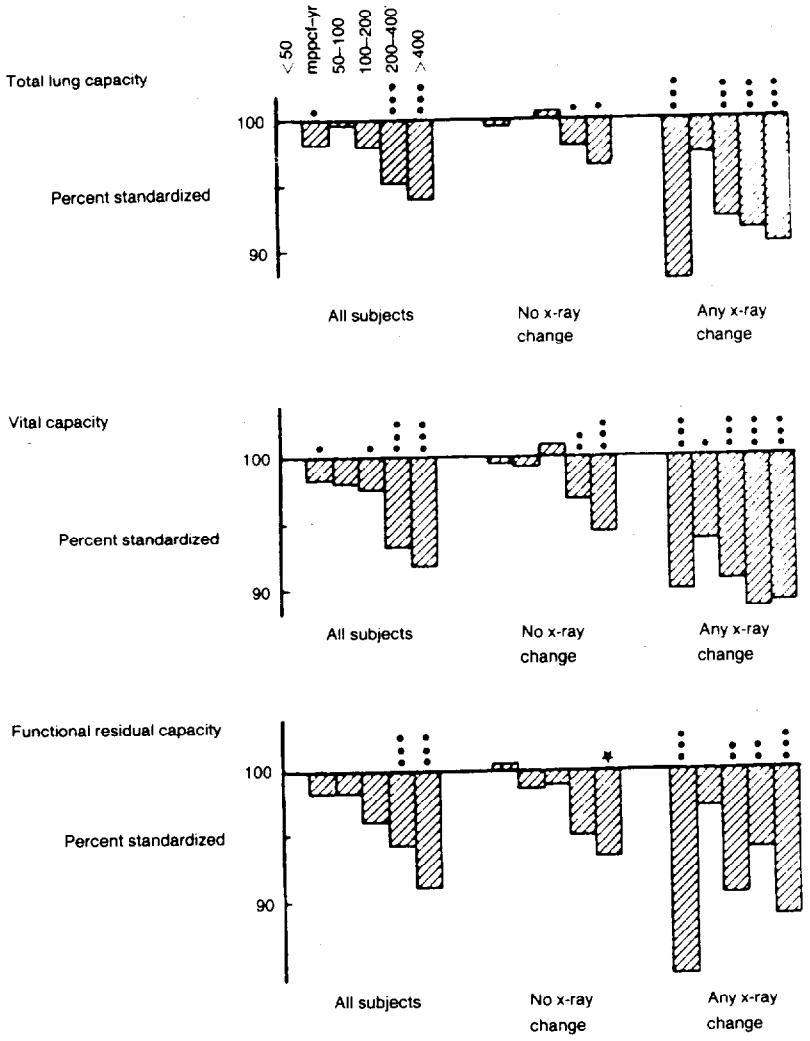

FIGURE 12.—Relationship between lung volumes and dust exposure

SOURCE: Weill et al. (1975).

Becklake et al. 1976). These workers were categorized as having a normal, undifferentiated, obstructive, or restrictive pulmonary function picture on the basis of a combined score of the percentage deviations from the predicted value of five pulmonary function tests

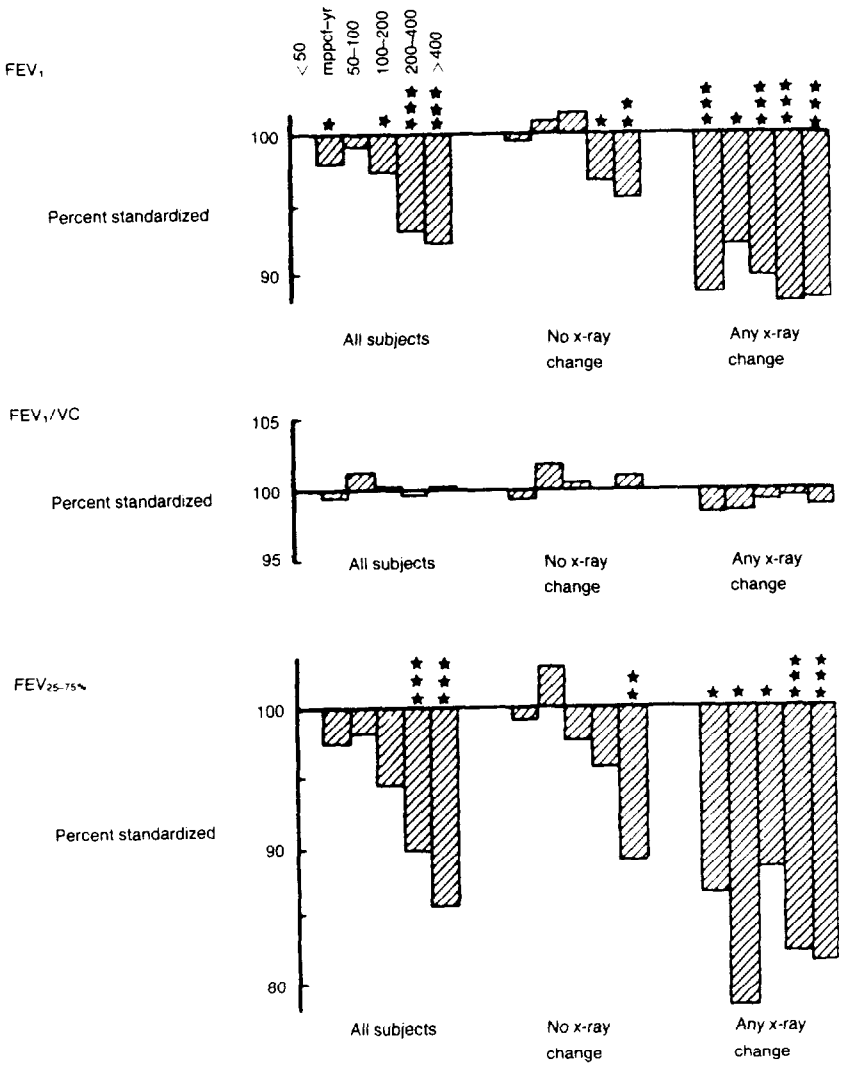

FIGURE 13.—Relationship between expiratory flow and dust exposure

SOURCE: Weill et al. (1975).

(Table 12). The deviation of the percentage predicted value was scored from 7 through 13 for each value, with lower numbers representing those measurements indicative of restrictive disease